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**Oxygen Delivery and Demand in
Conscious Pigs Subjected to
Fixed-Volume Hemorrhage and
Resuscitated With 7.5% NaCl in
6% Dextran**

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A conscious porcine model was used to investigate the adequacy of O₂ delivery relative to O₂ demand, initially during a fixed-volume hemorrhage (37.5 ml/kg over 1 hr) and subsequently after resuscitation with 7.5% NaCl/6% Dextran 70 (4 ml/kg). Hemorrhage produced a small increase in O₂ consumption, severe lactacidemia, and a doubling of apparent O₂ demand. These effects were attributable to a behavioral compensation (periodic bouts of muscle activity) which presumably served to improve venous return. Despite enhanced ventilatory function, arterial O₂ delivery was markedly reduced by hemorrhage, an effect that was due entirely to decrements in cardiac output and hemoglobin level. The disparity between O₂ delivery and O₂ demand was lessened following resuscitation with 7.5% NaCl/6% Dextran 70, primarily by suppression of demand and secondarily by an augmentation of delivery.

Key words: swine, hypertonic saline/dextran, O₂ transport, O₂ consumption, O₂ debt, lactacidemia, ventilation, cardiac output

INTRODUCTION

The level of blood loss experienced by combat casualties and civilian accident victims is frequently so severe that death ensues in the absence of prompt and

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effective therapy. In most instances, this therapy is directed at preventing further blood loss and implementing resuscitation procedures that reverse the life-threatening dysfunctions associated with hemorrhagic hypotension. Efforts to improve therapy, and thereby increase the survival incidence of hemorrhage victims, have been commonly based on experimental data, but oftentimes this information is misleading because inappropriate animal models have been used to study the functional effects of hemorrhage. Ideally, an animal model should simulate the physiologic conditions found in human hemorrhage victims, particularly when the research effort is directed at the development of an improved resuscitation procedure. Ethical constraints, e.g., the extensive trauma that so often accompanies severe blood loss in humans, preclude implementing an ideal model. At a minimum, however, the hemorrhage insult should emulate the rate and magnitude of blood loss seen in humans after vascular rupture; it should occur while the animal is in a conscious state to allow full and accurate expression of the normal physiologic changes associated with blood loss; and, if enhanced survival is an endpoint for evaluating efficacy of resuscitation, the hemorrhage insult should be lethal if left untreated. We hope to demonstrate the applicability of such a model in the present communication.

In several species, including pigs [1,2], sheep [3,4], and humans [5,6], small volume resuscitation with hypertonic saline/dextran (7.5% NaCl in 6% Dextran 70) effectively reverses many of the life-threatening dysfunctions associated with hemorrhage. It also provides significant improvement in the survival of animals subjected to lethal levels of blood loss [1,2]. The beneficial effects of hypertonic saline/dextran include a return of cardiac output and arterial pressure to normal or near normal values [1-4], an increase in blood flow to vital organs [7], and a restoration of urine production [3]. These functional improvements are attributable, at least in part, to fluid mobilization from the extra- to the intravascular compartment with consequent increases in blood volume and venous return [1-4]. It is tacitly assumed that the increases in cardiac output and tissue blood flow improve oxygen delivery to previously ischemic tissues, thereby ameliorating the lethal effects of hemorrhage. The validity of this assumption, however, can be questioned, at least insofar as conscious animals are concerned. Few data are available on the actual levels of arterial oxygen transport or tissue oxygen demand of conscious animals subjected to hemorrhage, and no one has investigated these variables following resuscitation with hypertonic saline/dextran. The study reported here was directed at these information deficits. It was a component of a much larger investigation which compared the resuscitative effectiveness of 0.9% NaCl, 7.5% NaCl, 6% Dextran 70, and 7.5% NaCl/6% Dextran 70 following administration to conscious chronically instrumented pigs that had been subjected to a lethal fixed-volume hemorrhage [1]. The present study had two specific objectives. The first was to determine the effects of this hemorrhagic insult on total body O_2 consumption, apparent O_2 demand and the various functional components of O_2 delivery from ambient air to the body tissues. The second objective was to determine, if possible, whether or not the resuscitative effectiveness of hypertonic saline/dextran was attributable solely to an improvement in O_2 delivery. Our data indicate that the lethality of the hemorrhage model is largely, if not entirely, due to a disparity between O_2 delivery and O_2 demand. Our data also indicate that the resuscitative effectiveness of hypertonic saline/dextran is attributable primarily to a suppression of tissue O_2 demand and secondarily to an improvement of O_2 delivery.

MATERIALS AND METHODS

Six immature (24.3 ± 1.11 kg, mean \pm SEM) Yorkshire pigs were used to investigate the effects of hemorrhage and resuscitation with hypertonic saline/dextran. Eight pigs (23.6 ± 1.87 kg) resuscitated with an equivalent volume of 0.9% NaCl served as hemorrhage controls, and eight additional pigs (26.1 ± 0.66 kg) were used as untreated controls for another simultaneously conducted investigation [8] as well as the investigation reported here. Seven to 10 days before study the pigs were splenectomized, and were chronically instrumented with carotid and pulmonary artery catheters and an aortic sideport catheter [9], as described in detail elsewhere [1]. During this same time period, they were trained to accept a respiratory mask and physical restraint in a Pavlov sling [1]. On the day of study, after an overnight fast, each pig was brought into a quiet laboratory, placed in the Pavlov sling, and fitted with the respiratory mask to measure respiratory functions. The mask was connected to a Horizons System metabolic apparatus using a one-way Rudolph valve and 2.5 cm (O.D.) plastic tubing. The pulmonary and carotid artery catheters were connected to three-way stopcocks for blood sampling, and to pressure tubing and transducers for measurements of hemodynamic function reported in detail elsewhere [1]. The animal was allowed to rest quietly in the sling until O_2 consumption values were maintained at minimal levels for 30 to 60 min. Control measurements for all experimental variables were then made in triplicate at 10 min intervals. Immediately thereafter, the aortic sideport catheter was opened, and a fixed-volume (37.5 ml/kg) hemorrhage schedule was initiated. Over a subsequent 60 min period, blood was removed progressively on an exponential scale [10] such that successive 7.5 ml/kg increments had been withdrawn after 9, 19, 31.5, 44, and 60 min. At each of these time points all measurements were repeated. Immediately after hemorrhage, the animal received a 4 ml/kg mixture of 7.5% NaCl/6% Dextran 70, injected into the pulmonary artery over a 1-min time interval. Hemorrhage controls received 4.0 ml/kg of 0.9% NaCl. All measurements were again taken at 5, 15, 30, 60, 120, 180, and 240 min after the cessation of hemorrhage.

At each measurement point, a 30 ml blood sample was removed from the carotid artery and a 3 ml sample from the pulmonary artery; samples taken during the control and hemorrhage periods were included in hemorrhage volume. These samples were chilled in ice water and then partitioned for a variety of subsequent determinations. The latter included immediate measurement of O_2 content and hemoglobin concentration with an Instrumentation Laboratory Model 282 Cooximeter. Plasma lactate concentration was determined with a GEMSAEC autoanalyzer and Sigmasytem test kits. At all of the foregoing time points, expired ventilation was recorded BTPS, and O_2 consumption and CO_2 production STPD. On the basis of the foregoing measurements, cardiac output values were calculated by the Fick equation, and arterial oxygen delivery as the product of arterial O_2 content and cardiac output. Changes in plasma lactate concentration as a function of time were used to calculate apparent O_2 debt. In making these calculations it was assumed that 1 mol of O_2 was required to convert 2 mol of lactate to pyruvate [11]. It was also assumed that plasma lactate concentration reflected the average concentration in total body water; a value of 640 ml/kg, as determined by 3H_2O dilution [12], was chosen for the latter. The sum of O_2 consumption and O_2 debt was used to estimate apparent O_2 demand of the tissues. In addition, alveolar ventilation (V_A) values were calculated by the Bohr equation:

$$V_A = \frac{(0.867)(VCO_2)}{P_aCO_2}$$

where 0.867 is a constant that converts VCO_2 from STPD to BTPS, assuming a normal porcine body temperature of 38.5°C. The shunt fraction of pulmonary blood flow (Q_s) was calculated by a modification of the Fick equation:

$$\frac{Q_s}{Q_T} = \frac{C_eO_2 - C_aO_2}{C_eO_2 - C_vO_2}$$

Here Q_T is cardiac output, C_eO_2 is pulmonary end capillary O_2 content, C_aO_2 is arterial O_2 content, and C_vO_2 is mixed venous O_2 content. Temperature and Bohr factors appropriate for the oxyhemoglobin dissociation curve of porcine blood, as reported by Willford and Hill [13], were used in the calculation of C_eO_2 values. Finally, alveolar ventilation and cardiac output values were used to calculate ventilation-perfusion ratios, i.e., V_A/Q_T .

Two factor (treatment, time) and single factor (time) analyses of variance were used as appropriate for within- and between-group comparisons. The single factor evaluation of pigs resuscitated with 7.5% NaCl/6% dextran was first applied to the hemorrhage period and then to the first hour of the recovery, i.e., before any of the animals had died. Changes were considered significant when $P \leq 0.05$. In addition, mean \pm S.E.M. values were calculated for each time point during control, hemorrhage, and recovery periods. At 1 hr and thereafter during the recovery period, two mean values were calculated for the time point that preceded death of an animal: one mean included and the other excluded the nonsurviving animal. This double calculation was directed at minimizing data distortion that might result from changes in interanimal variance associated with a reduction in group size. Representative S.E.M. values are indicated in the figures that follow.

RESULTS

The responses of the control and experimental groups to hemorrhage alone were not significantly different. Resuscitation with 0.9% NaCl, however, was ineffective, and all of these controls died shortly after the resuscitation procedure was initiated [1]. Nonsurvival of these animals precluded statistical evaluation of their resuscitation data. Untreated control pigs showed only one significant functional change during a 4 hr period of continuous restraint; the respiratory exchange ratio decreased slightly (Table I). The functional data recorded in these animals were nearly identical to control (0 time) data recorded in animals subjected to hemorrhage.

Hemorrhage produced a small, progressive increase in O_2 consumption, the average values rising significantly from a control level of 6.9 ± 0.51 to 9.5 ± 0.73 ml/min/kg at the end of blood removal (Fig. 1A). This effect was associated with periodic bouts of muscle activity (leg movements and stretching). During recovery following resuscitation with hypertonic saline/dextran, O_2 consumption reverted rapidly (within 30 min) to control levels. Over the course of hemorrhage, the respiratory exchange ratio rose from 0.79 ± 0.036 to 1.06 ± 0.094 , presumably as a consequence of hyperventilation.

Plasma lactate concentration (not shown), rose significantly during hemorrhage, from 0.6 ± 0.04 to 13.6 ± 1.03 mEq/L. When calculated in terms of O_2 equivalents,

TABLE I. Effects of Continuous Restraint in a Pavlov Sling on the Metabolic, Ventilatory, and Cardiovascular Functions of Conscious Pigs[†]

	0	5	10	Restraint time (min)				
				60	120	180	240	
O ₂ Consump. (ml/min/kg)	6.7 ± 1.9	7.0 ± 1.5	7.2 ± 2.2	7.4 ± 2.3	6.4 ± 1.4	6.2 ± 1.0	8.0 ± 1.5	6.8 ± 1.4
Resp. exchange ratio*	0.79 ± 0.06	0.81 ± 0.03	0.78 ± 0.03	0.77 ± 0.05	0.78 ± 0.08	0.75 ± 0.08	0.72 ± 0.04	0.73 ± 0.04
Expir. vent. (ml/min/kg)	195 ± 48	207 ± 24	266 ± 55	218 ± 63	207 ± 52	175 ± 38	217 ± 38	192 ± 42
Resp. rate (br/min)	23 ± 3	22 ± 5	23 ± 3	23 ± 1	23 ± 2	21 ± 3	23 ± 3	24 ± 3
Alv. vent. (ml/min/kg)	97 ± 22	100 ± 16	105 ± 31	97 ± 28	104 ± 31	79 ± 33	100 ± 24	104 ± 17
Card. output (ml/min/kg)	141 ± 36	150 ± 32	116 ± 42	137 ± 56	137 ± 45	117 ± 46	153 ± 62	138 ± 23
V _A /Q _T	0.68 ± 0.11	0.69 ± 0.14	0.66 ± 0.15	0.72 ± 0.13	0.73 ± 0.18	0.67 ± 0.14	0.63 ± 0.13	0.67 ± 0.15
Q _S /Q _T (%)	3.8 ± 3.0	3.6 ± 3.0	5.4 ± 3.6	1.8 ± 1.1	4.1 ± 4.0	3.2 ± 2.3	6.3 ± 4.3	3.5 ± 2.4
Hemoglobin (g/dl)	9.6 ± 0.9	9.1 ± 0.9	9.6 ± 0.8	9.8 ± 1.0	9.7 ± 1.1	9.6 ± 1.0	9.4 ± 0.9	9.9 ± 1.0
Art O ₂ cont. (ml/dl)	12.9 ± 1.9	13.0 ± 2.3	13.0 ± 1.8	12.9 ± 1.7	12.7 ± 1.6	12.6 ± 1.6	12.1 ± 1.1	12.4 ± 1.3
Ven. O ₂ cont. (ml/dl)	7.8 ± 1.3	7.3 ± 1.4	6.8 ± 1.5	6.8 ± 1.0	6.9 ± 1.5	7.5 ± 1.2	6.7 ± 1.5	6.5 ± 1.5
Art O ₂ deliv. (ml/min/kg)	18.7 ± 4.7	20.0 ± 3.8	15.5 ± 4.8	18.6 ± 9.3	18.2 ± 6.5	15.7 ± 7.5	19.4 ± 8.4	17.7 ± 2.6
Plasma lact. (mEq/L)	0.60 ± 0.13	0.48 ± 0.19	0.51 ± 0.23	0.48 ± 0.22	0.45 ± 0.20	0.42 ± 0.18	0.46 ± 0.18	0.50 ± 0.17

† Indicated values represent the Mean ± S.D. of 8 pigs.

*Significant ($P \leq 0.05$) change as a function of time.

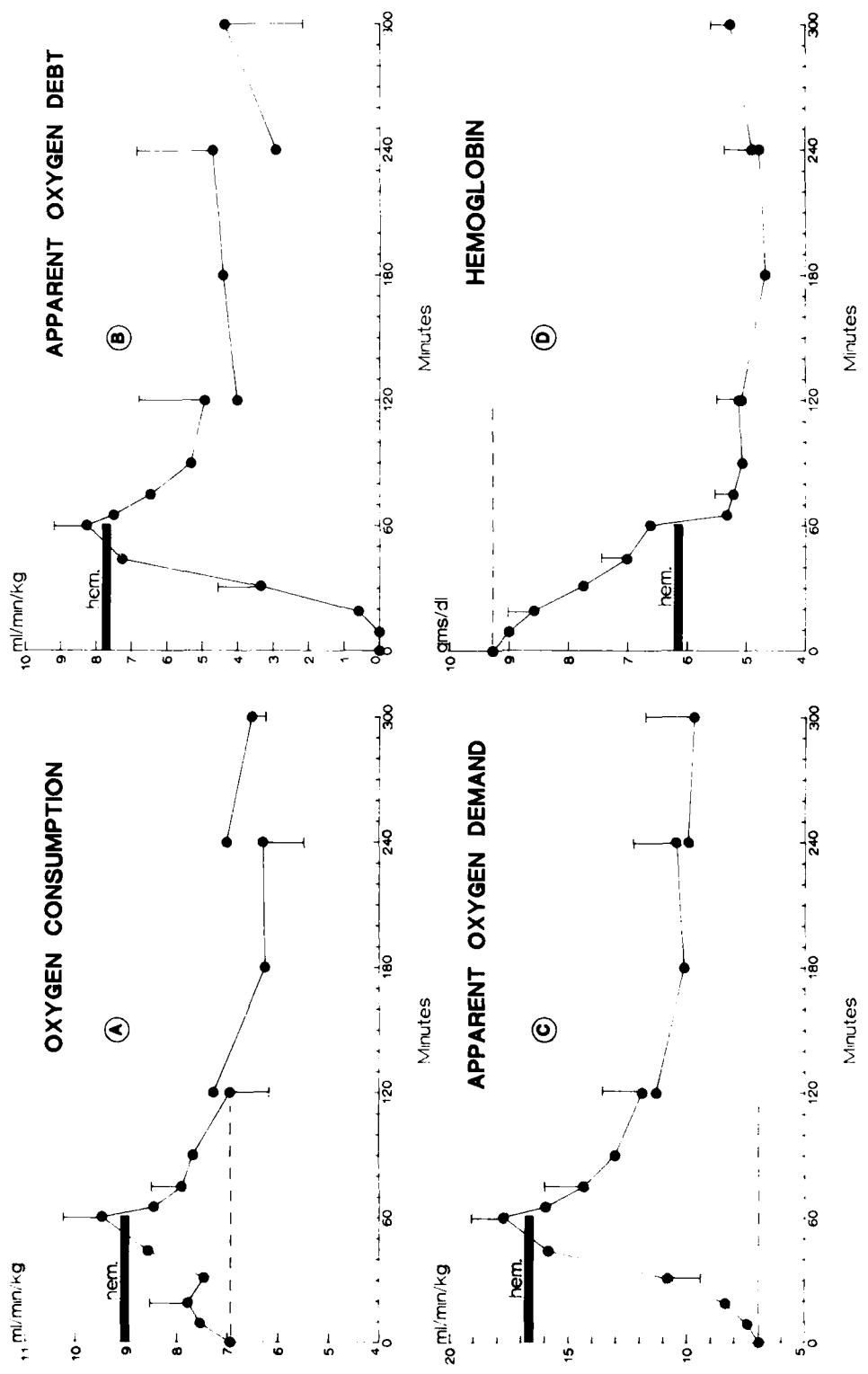


Fig. 1.

this rise represented an absolute O_2 debt of approximately 100 ml/kg. When calculated as a function of time, the apparent O_2 debt thus rose progressively, to 8.25 ± 0.87 ml/min/kg at the end of hemorrhage (Fig. 1B). These changes led in turn to a significant increase in apparent tissue O_2 demand from a control level of 6.94 ± 0.51 to 15.82 ± 2.36 ml/min/kg (Fig. 1C). Resuscitation with hypertonic saline/dextran produced a significant reversion of O_2 consumption to control levels and a significant resolution of the increments in apparent O_2 debt and O_2 demand that accrued during hemorrhage.

The hemoglobin concentration of arterial blood decreased significantly during hemorrhage from 9.3 ± 0.46 to 6.6 ± 0.37 g/dl (Fig. 1D); it might be noted, incidentally, that the low control values for hemoglobin and related variables (e.g., O_2 content) reported here are typical of immature pigs [10]. Following administration of 7.5% NaCl/6% dextran, an abrupt further significant decrease to 5.3 ± 0.32 g/dl was observed at 5 min into the recovery period. Thereafter, hemoglobin concentration remained relatively stable.

Hypermetabolism during hemorrhage was supported by increased ventilation, the expired values rising significantly from 208 ± 23.9 to 506 ± 61.3 ml/min/kg (Fig. 2A). This response was accompanied by a significant rise in alveolar ventilation from 120 ± 12.4 to 214 ± 32.2 ml/min/kg (Fig. 2B). Hyperventilation was largely, if not entirely, attributable to a significant increase in respiratory rate, from 19 ± 1.9 to 37 ± 4.2 breaths/min (Fig. 2C). Thus, tidal volume (Fig. 2D) rose only slightly during hemorrhage from 10.6 ± 0.77 to 13.8 ± 1.16 ml/min/kg, a change that was not statistically significant. Expired ventilation and alveolar ventilation decreased gradually, but significantly, following resuscitation, and the values approached control levels at 4 hr into the recovery period.

The combined effects of an increase in alveolar ventilation and a decrease in cardiac output (see below) led to a marked increase in the ventilation:perfusion ratio (V_A/Q_T) from 0.68 ± 0.048 to 2.15 ± 0.195 (Fig. 2E). The decrease in cardiac output also caused a significant reduction in pulmonary shunt fraction (Q_S/Q_T) from 6.4 ± 0.42 to 1.4 ± 0.28 (Fig. 2F). Resuscitation with hypertonic saline/dextran produced an immediate and almost complete reversion of the V_A/Q_T ratio toward control levels. The Q_S/Q_T ratio, in contrast, was not altered significantly following resuscitation.

Hemorrhage also led to significant decrements in the O_2 content of arterial (from 11.7 ± 0.64 to 8.6 ± 0.49 ml/dl, Fig. 3A) and mixed venous (from 7.6 ± 0.63 to 0.97 ± 0.20 ml/dl, Fig. 3B) blood. The more pronounced change in mixed venous O_2 content resulted in a significant widening of the A-V difference, from 4.0 ± 0.16 to 7.7 ± 0.41 ml/dl (Fig. 3C). Resuscitation with hypertonic saline/dextran had a significant effect on all of these variables: at 5-min into the recovery period arterial O_2 content was further reduced to 6.8 ± 0.40 ml/dl, mixed

Fig. 1. Effects of progressive fixed-volume hemorrhage (37.5 ml/kg) followed by resuscitation with 7.5% NaCl/6% dextran on total body energy metabolism and hemoglobin level of conscious swine ($n = 6$). Resuscitation (4 ml/kg) was provided immediately (over 1 min) after hemorrhage. Breaks in the plots indicate time points at which mean and S.E.M. values were calculated to include as well as exclude an animal that died shortly thereafter. Solid bar depicts the hemorrhage interval, dashed bar the control level for each variable. Significant effects ($P < 0.05$) are indicated in text.

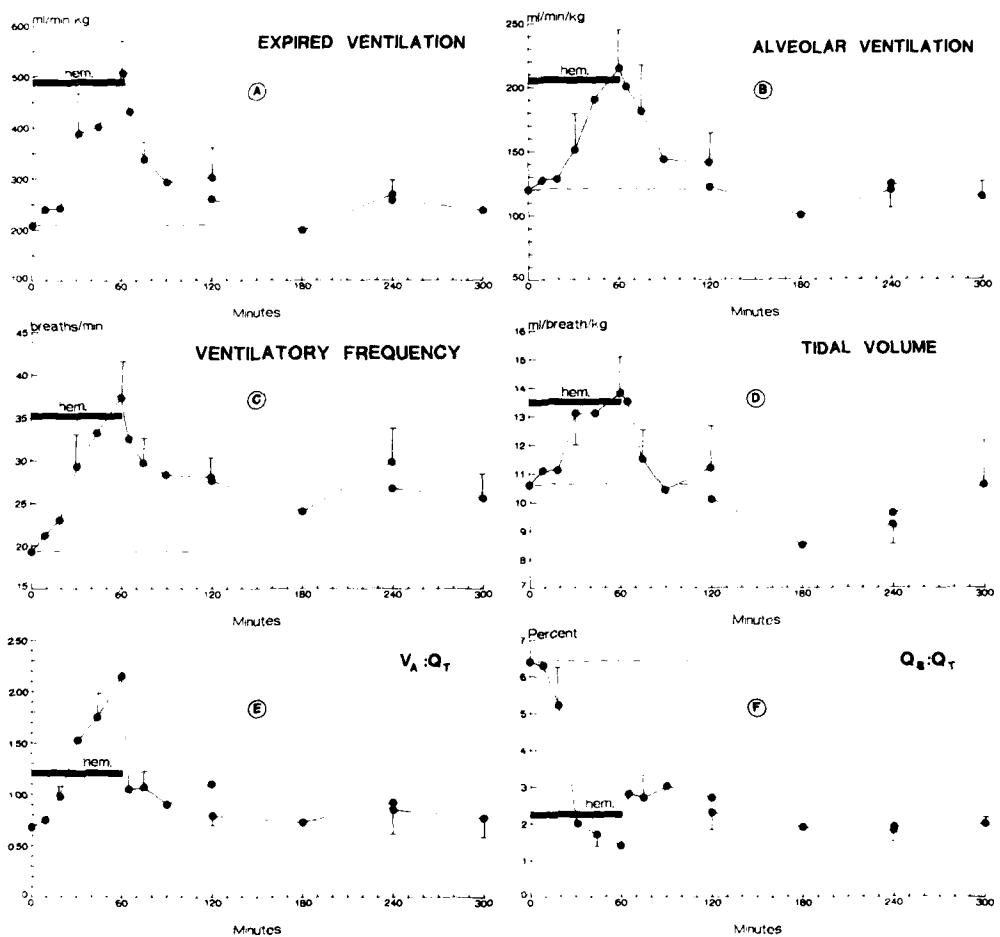


Fig. 2. Effects of progressive fixed-volume hemorrhage (37.5 ml/kg) followed by resuscitation with 7.5% NaCl/6% dextran on pulmonary functions of conscious swine. See Figure 1 for other experimental details.

venous O_2 content was raised to 2.5 ± 0.50 ml/dl, and the A-V O_2 difference was reduced to 4.3 ± 0.39 ml/dl. The A-V difference was no different from that observed under control conditions. These acute effects of hypertonic saline/dextran were maintained with little change over the subsequent course of recovery.

A significant decrease in cardiac output during hemorrhage (from 177 ± 15.6 to 98 ± 13.9 ml/min/kg, Fig. 3D) combined with the above-indicated reduction in arterial O_2 content led to a significant reduction in arterial O_2 delivery (from 20.9 ± 2.39 to 9.3 ± 1.14 ml/min/kg, Fig. 3E). As a consequence of these changes, the ratio of O_2 delivery to apparent O_2 demand was reduced significantly from 2.96 ± 0.192 to 0.52 ± 0.055 (Fig. 3F). In short, O_2 delivery supported about one-half of the O_2 demand.

Resuscitation with hypertonic saline/dextran led to a marked and significant increase in cardiac output to 202 ± 19.0 ml/min/kg at the 5 min point during the

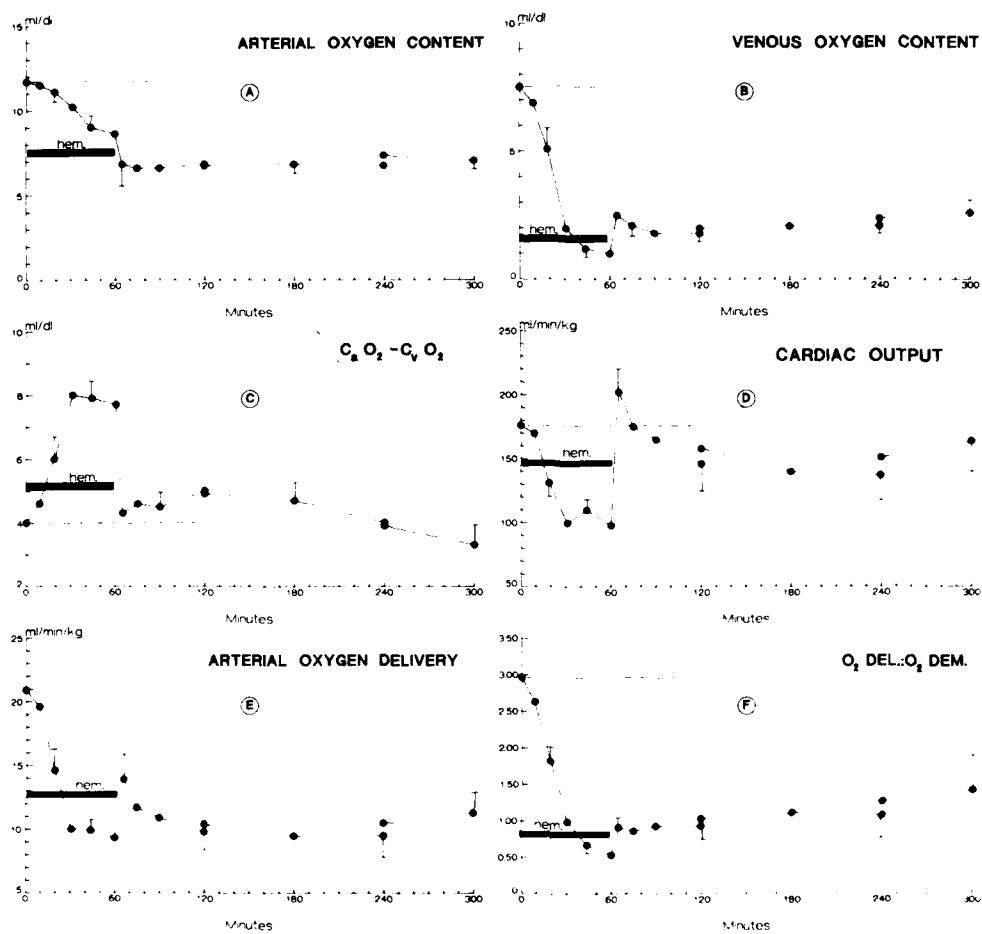


Fig. 3. Effects of progressive fixed-volume hemorrhage (37.5 ml/kg) followed by resuscitation with 7.5% NaCl/6% dextran on blood oxygen delivery of conscious swine. See Figure 1 for other experimental details.

recovery period. This elevation, however, was not sustained, and after 30–60 min the values stabilized at about 80% of the control level. Arterial O₂ delivery showed only transient, and far from complete recovery following administration of 7.5% NaCl/6% dextran. During most of the recovery period the values were essentially the same as those recorded at the end of hemorrhage. The ratio of O₂ delivery to apparent O₂ demand showed a small but significant improvement following hypertonic saline/dextran administration, an effect that was sustained over the remainder of the recovery period.

DISCUSSION

The foregoing data show that an increasing disparity between O₂ delivery and O₂ demand presents a major threat to the survival of conscious pigs subjected to

severe blood loss. Oxygen delivery was compromised by a progressive decrease in both arterial O_2 content and cardiac output. The decrements in O_2 content were attributable to transcapillary refill which reduced hemoglobin concentration and blood O_2 capacity. The decrements in cardiac output values were due to a progressive fall in blood volume with a consequent decrease in venous return [1]. Normal compensations were ineffective in addressing the defect in arterial O_2 delivery. Hyperventilation raised arterial PO_2 , but the potential benefit was negated by hemoglobin dilution. Benefit from increased O_2 extraction, as evidenced by a widening of the A-V difference in O_2 content, was limited by venous O_2 content reaching minimal values (<1 ml/dl) during the last half of the hemorrhage episode. As a consequence, apparent oxygen demand rose markedly and eventually exceeded O_2 delivery by a factor of at least two. When unchecked by effective resuscitation, the disparity between O_2 delivery and O_2 demand became progressively more pronounced and eventually led to uncompensated acidosis, hypoventilation, myocardial failure, hypometabolism, and a consistently lethal outcome [1].

On the basis of subjective evidence, it appeared that the hemorrhage-induced increase in metabolic rate was due to physical activity (leg movements, stretching, etc.), since cyclical increases in O_2 consumption coincided with periodic bouts of muscle activity; hyperventilatory work and elevated sympathetic activity may have been contributing factors. Skeletal muscle activity, in our opinion, reflected a behavioral compensation for hemorrhage and served, presumably, to enhance venous return as blood volume was reduced. Such a compensatory response has not been reported previously, insofar as we are aware, perhaps because of constraints inherent in the animal models or procedures that were used in earlier studies of energy metabolism during hemorrhage. Indeed, most [14-22] but not all [23-25] previous reports show that hemorrhage leads to an unchanged [23-25] or reduced [14-22] O_2 consumption. It is perhaps significant that the majority of these investigations involved animals that were anesthetized, mechanically ventilated, subjected to a rapid and sustained reduction in blood pressure (Wiggers procedure), or a combination of these variables. One would not expect to see muscle activity with a consequent increase in the O_2 consumption of chemically restrained animals, and normal compensatory responses could be overwhelmed or go unobserved in conscious animals subjected to rapid blood loss or the Wiggers procedure. Only Nahas et al. [26] have found metabolic increments similar to those reported here. Their results were obtained with anesthetized dogs subjected to a relatively modest, fixed-volume, hemorrhage (25 ml/kg) over a 30 min period with arterial pH maintained within 0.1 unit of 7.40. They [26] attributed the hypermetabolic effect of hemorrhage to sympathetic activation, catecholamine release, and a resultant stimulation of free fatty acid oxidation. This calorogenic effect of catecholamines was observed only in the absence of acidosis [26]. Data recorded in the present study, or obtained coincidentally, are consistent with the observations and interpretations of Nahas et al. [26]. Hyperventilation and the blood buffer system effectively compensated for elevated lactic acid production (arterial pH did not change significantly) while plasma concentrations of both epinephrine and norepinephrine rose markedly [27].

It seems probable that our calculated values for apparent O_2 debt underestimate the true values because one or both of two underlying assumptions were not totally valid. One of these assumptions is that lactate is uniformly distributed in total body

water. Lactate is known to be readily diffusible in body fluids [28], but it seems likely that higher concentrations would be found in tissues rendered ischemic by hemorrhage (e.g., skeletal muscle, skin, viscera) than those protected from ischemia by a preferential redistribution of cardiac output (e.g., heart, brain). If the total mass of ischemic tissue exceeds that of non-ischemic tissue, as it probably does in severe hemorrhage, then the lactate concentration of plasma would underestimate the average concentration in total body water.

The second assumption is that elevated lactic acid production is totally responsible for the O_2 debt associated with hemorrhage. It is now well established [11] that the reduction of pyruvate to lactate conserves 1/2 mol (11.2 ml/mmol) of oxygen for every mole of lactate produced and, conversely, that oxidation of lactate to pyruvate requires 1/2 mol of oxygen for every mole of pyruvate produced. This latter requirement has served as the basis for numerous studies directed at the reliability of plasma lactate, or excess lactate, as a predictor of the total body O_2 debt. Some workers [29] find a poor relationship between O_2 debt and exercise-induced lactacidemia, whereas others [30,31] report an excellent correlation. The level of lactacidemia appears to be the critical variable; the heavier the work load, the better the correlation [30,31]. Cain [32] reports similar results and conclusions when hypoxia is used to induce an O_2 debt. The lactate levels seen in the present study at the end of hemorrhage were comparable to those reported for heavy work by Knuttgen [30] and Wasserman et al. [31], hence a comparable O_2 debt might be anticipated. However, it is also well established [11,28,30-32] that measured values for O_2 debt always exceed those calculated from plasma lactate, or excess lactate. The discrepancy is due to the presence of an "alactacid" debt [11,33], which includes decrements in the O_2 stores normally contained in the lungs, body fluids, hemoglobin, and myoglobin, a degradation of high-energy phosphates, and other as yet unidentified variables. Correction of these alactacid changes requires O_2 consumption over and above that predicted by plasma lactate or excess lactate alone.

The functional mechanisms responsible for the salutary effects of hypertonic saline/Dextran 70 are not totally clear, at least in terms of the factors contributing to the adequacy of O_2 delivery relative to tissue O_2 demand. On the delivery side, the improvement in cardiac output shortly after administration of hypertonic saline/dextran was consistent with the reports of others [2-4,7]. The consequent enhancement of arterial O_2 transport, however, was unimpressive, because fluid mobilization during resuscitation produced a sharp decrease in hemoglobin level and thus blood O_2 capacity.

Suppression of O_2 demand following hypertonic saline/dextran resuscitation appeared to be a far more important determinant of survival. It was a major factor underlying return of A-V differences in O_2 content to normal levels, a change that indicated adequacy of O_2 delivery relative to demand. The functional changes responsible for the suppression of O_2 demand, however, were not totally resolved in the present study. O_2 demand was clearly associated with a decrease in muscle activity, but other factors also may have been involved. For example, Nahas and his coworkers [26] showed that acidosis caused a reduction in O_2 consumption during hemorrhage and attributed this effect to an inhibition of catecholamine calorigenesis. Such effects would not be inconsistent with our observations on the actions of hypertonic saline/dextran. Accordingly, other measurements made on these pigs

showed a sharp reduction in arterial pH [29] and plasma catecholamine levels [27] shortly after the administration of hypertonic saline/dextran. The interactions of these and other related variables obviously need further investigation.

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The experiments described in this paper were performed in adherence to the NIH guidelines for the use of experimental animals.

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